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BUDAPEST

---------- Translated from Hungarian ----------

---------- HUNGARIAN REPUBLIC ----------

---------- PRIORITY CERTIFICATE ----------

Serial No. ----------

P0202001 ----------

The National Office of Inventions certifies that --
Sanofi-Synthelabo, Paris (FR), ----------
filed a patent application in Hungary on 14 June 2002 ----------
under registration No. 24988/02, entitled --------
New compounds ----------
The attached copy is fully identic with the papers filed simultaneously with the application. -------
Budapest, 16 June 2003 ----------
Illegible signature ----------
Signed and issued by: ----------
Szabó Emilné Deputy Head of Patent Department ----
The Hungarian Patent Office certifies in this priority certificate that the said applicant(s) filed a patent application at the specified date under the indicated title, application number and registration number. The attached photocopy is a true copy of specification filed with the application. -
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The enzyme, dipeptidyl-peptidase-IV (DPP-IV), identical with the lymphocyte surface glycoprotein CD26, a polypeptide with 110 k Dalton molecular mass, is formed in the tissues and organs of mammals. This enzyme can be found among others in the liver, in the Langerhans islands of the pancreas, in the renal cortex, in the lungs, and in certain tissues of the prostate and small intestine. Significant DPP-IV activity can be observed furthermore in the body liquors (like plasma, serum and urine). ----------

DPP-IV is a serine protease type enzyme, which has the unique specificity to cleave dipeptides from the N-terminals of the peptides, where the pre-terminal dipeptide is prolylalanine, or the pre-terminal amino acid is hydroxyproline. ----------

DPP-IV enzyme is responsible for the decomposition of the glucagon-like, peptide-1 (GLP-1) and peptide-2 (GLP-2) in the body. The enzyme GLP-1 strongly stimulates the insuline production of the pancreas, having thus a direct, favourable effect on glucose homeostasis, therefore the DPP-IV inhibitors are suitable for the treatment of non-insuline dependent diabetes mellitus (NIDDM). There are a number of DPP-IV inhibitors known in

the literature, but they have disadvantages as regards their activity, toxicity and stability. ----
Our aim was to prepare new, effective and safe DPP-IV inhibitors. ----------
We have found that the compounds of the general formula (I) wherein R^1 stands for: ----------
- nitrogen-containing one- or two-membered aromatic rings, preferably a pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, imidazolyl, pirazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, benzimidazolyl, indazolyl, benzothiazolyl, benzisothiazolyl, benzoxazolyl or benzisoxazolyl group, optionally mono- or disubstituted independently by one or two of the following groups: C1-4 alkyl group, C1-4 alkoxy group, a halogen atom, a trihalogenomethyl group, methylthio group, nitro group, cyano group, or; ----------
- an R_{1a}-CH_2-group, where the meaning of R_{1a} is a hydrogen, a C1-4 alkyl group, or phenyl, benzyl, phenylethyl, phenylethenyl, naphthyl, pyridyl, quinolyl, isoquinolyl, cinnolinyil, phthalazinyl, quinazolinyl, quinoxalinyl, thienyl, furyl or *p*-tolylsulfonyl groups substituted independently by

one or more C1-4 alkyl, C1-4 alkoxy, alkylenedioxy, halogen, trihalogenomethyl, nitro or cyano group, or ----------

- an R_{1b}-CO-group, where the meaning of R_{1b} is C1-4 alkyl group, or phenyl, benzyl, phenylethyl, phenylethenyl, naphthyl, pyridyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl or quinoxalinyl groups substituted independently by one or more C1-4 alkyl, C1-4 alkoxy, alkylenedioxy, halogen, trihalogenomethyl, nitro or cyano group; mono- or disubstituted amino group, saturated *N*-containing heterocyclic ring, preferably a group containing pyrrolidine, piperidine, piperazine or morpholine ring, ----------

- m means 2 or 3, ----------

- Z stands for a group of formula (1), (2), (3), (4), (5), (6), (7) or (8); ----------

and the salts, isomers or solvates of the above compounds possess remarkable advantages regarding their activity, stability and toxicity. ----------

In accordance with the accepted terminology, the configuration of the carbon atom adjacent to the nitrogen of the N-containing pentacyclic ring is favourably *R* if Z stands for formula (1), and favourably *S* if Z stands for formula (2), (3), (4),

(5), (6), (7) or (8). In the case of compound (4) the methyl group, in the case of compound (6) the benzyloxy group, and in the case of compound (7) the hydroxy group is in *trans* position in relation to the cyano group. ----------

Especially advantageous are the compounds wherein the meaning of R^1 is a 2-pyridazyl or 2-pyridyl group substituted with a nitro or cyano group and Z stands for formula (1); such compounds are for instance 3-{[8-(5-cyanopyridin-2-yl)-8-azabicyclo-[3.2.1]octan-3-yl]-*exo*-amino}acetyl-4-(R)-cyan- --othiazolidine and 3-{[8-(pyrazin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl]-*exo*-amino}acetyl-4-(R)-cyan-othiazolidine, or if the meaning of Z is formula (2), 3-{[8-(5-nitropyridin-2-yl)-8-azabicyclo- ---[3.2.1]octan-3-yl]-*exo*-amino}acetyl-4-(S)-cyano- --pyrrolidine. ----------

The compounds of the general formula (I) according to our invention - wherein the meanings of R^1 and m are as defined above - can be prepared by alkylation of the cyclic primary amines of the general formula (II) with the chloroacetyl derivatives of the general formula (III) - wherein the meaning of Z is as defined above - and, if desired, the resulting compounds are transformed into a salt or a

solvate (Figure 1.). ----------

In the course of alkylation the chloroacetyl derivatives of the general formula (III) are applied in excess, and the resulting hydrogen chloride is bound by various acid-binding agents, preferably by a various bases, like 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU), triethylamine, potassium carbonate or 2-*terc*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (PBEMP) which is bound to a resin and is known as super base. The reaction is preferably performed at a temperature between 25 and 75 °C during 3-16 hours. ----------

The cyclic primary amines of the general formula (II) are prepared in a two-step synthesis (Figure 2.). In the first step the starting cyclic secondary amines of the general formula (IV) containing the acylamido side-chain - wherein Y means preferably an acetyl or *tert*-butoxycarbonyl group -, is arylated. Depending on the meaning of R^1, arylation can be performed in a polar, a protic or an aprotic solvent, preferably in an alcohol (ethanol, *n*-butanol, *n*-pentanol), at a temperature between 78 and 136 °C, or without solvent, in a microwave oven, using excess amine or DBU as acid

binder. ----------

In the second step the protecting Y group is removed by acidic hydrolysis from the arylated amines of the general formula (V) - wherein the meanings of R^1 and Y are as defined above. The reaction is carried out in aqueous hydrochloric acid or in hydrogen chloride solution in ethanol during 3-8 hours at a temperature between 25 and 78 °C, to produce the cyclic primary amines of the general formula (II) - wherein the meaning of R^1 and m is the same as defined above. ----------

In cases where R^1 is a R_{1a}-CH_2- or R_{1b}-CO-group, the compound of the general formula (IV) - wherein the meaning of Y is a *tert*-butoxycarbonyl group - is reacted with a compound of the general formula R_{1a}-CH_2X or R_{1b}-COX - wherein the meaning of Y is a leaving group, preferably a chloro atom - favourably at a temperature around 0 °C, using an inorganic or organic base, preferably triethylamine as acid binding agent. From the resulting compounds of the general formula (V) the protecting Y group is split off under acidic conditions, preferably by trifluoroacetic acid in dichloromethane solution, at a temperature between 0 °C and 30 °C, obtaining thus the compounds of the general formula

(II) - wherein the meaning of R_1 is a R_{1a}-CH_2- or a R_{1b}-CO-group. ----------

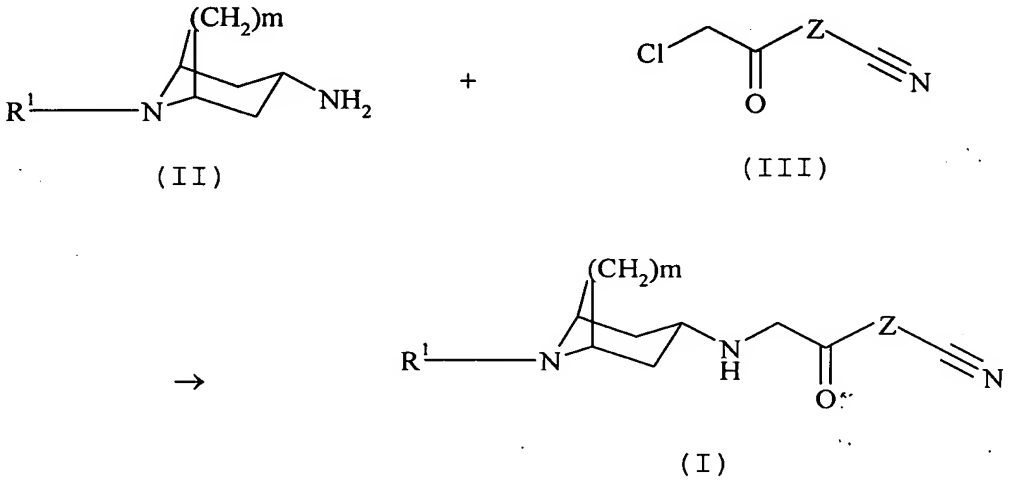
------- The chloroacetyl compounds of the general formula (III) - wherein the meaning of Z is as defined above - are prepared in a four-step synthesis (Figure 3.). ----------

------- The starting compounds are the N-containing pentacyclic carboxylic acids of the general formula (VI) - wherein the meaning of Z is as defined above, with the nitrogen protected with a *tert*-butoxycarbonyl group. These compounds can be purchased (group Z = (2); Aldrich), or prepared (Z = (1): Kitcin et al. J. Med. Chem. 37, p. 3712 (1994), Z = (3) and (4); S. Conti et al. Tetrahedron. 50, p. 13493 (1994); Z = (5): S.C. Mayer et al. J. Org. Chem. 59, p. 5192 (1994); Z = (6): M.G.N. Russel et al. Bioorg. Med. Chem. Lett. 9, p. 2491 (1999)). In the first step a mixed anhydride is prepared with pivaloyl chloride, then the carbamoyl derivatives of the general formula (VII) - wherein the meaning of Z is the same as defined above - are formed with aqueous ammonia. The reaction is preferably carried out in a halogenated solvent ($CHCl_3$, CH_2Cl_2) at 15 °C during 2-4 hours. ----------

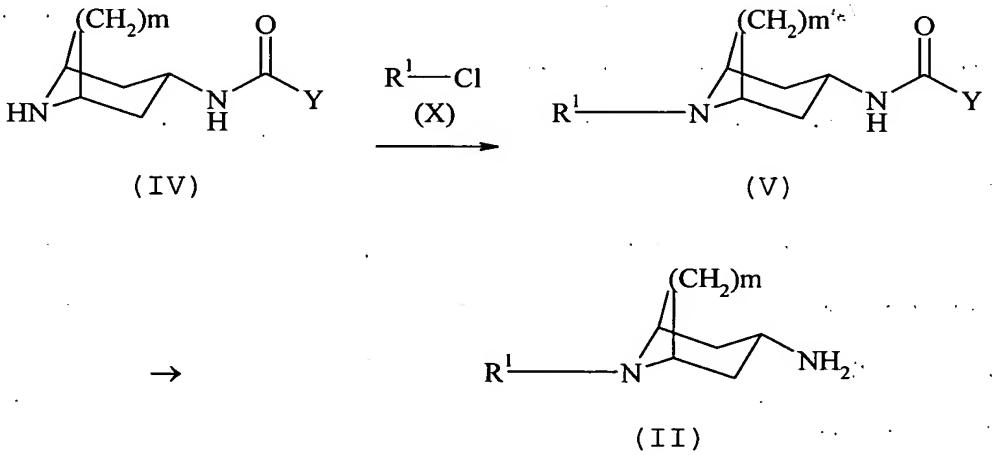
------- In the second step the *tert*-butoxycarbonyl group is removed by hydrolysis in hydrogen chloride solution in ethanol at 0 - 25 °C during 3-5 hours, obtaining hydrochlorides of the carboxamides of the general formula (VIII) - wherein the meaning of Z is the same as defined above. -------

------- The resulting pentacyclic saturated carboxamides of the general formula (VIII) are in the third step acylated with chloroacetyl chloride, preferably at 0 °C in a halogenated solvent ($CHCl_3$, CH_2Cl_2) for 2-4 hours to obtain the chloroacetylcarbamoyl derivatives of the general formula (IX) - wherein the meaning of Z is the same as defined above. ----------

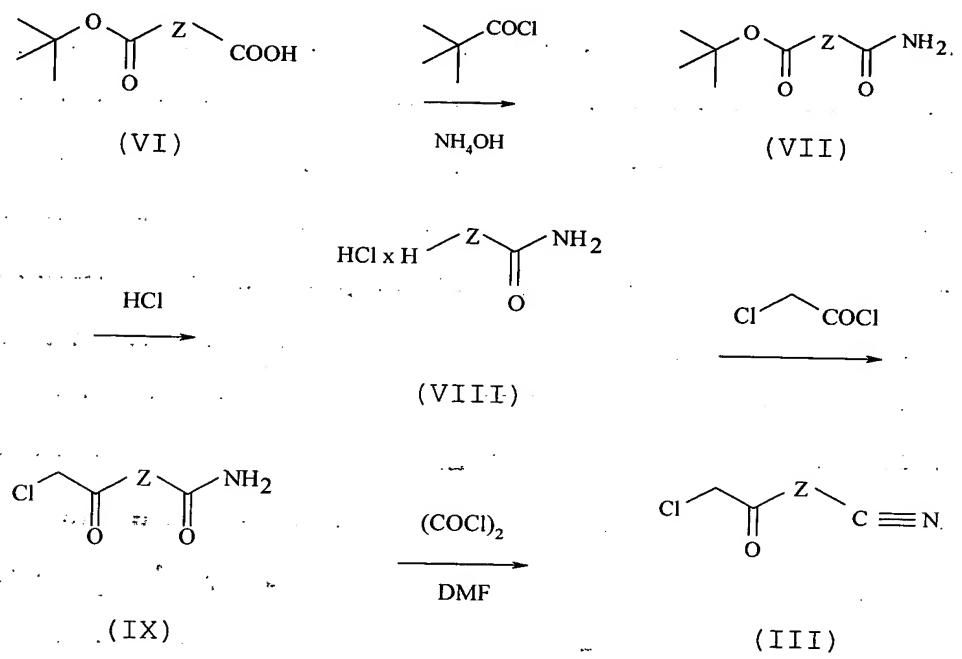
------- In the fourth step the chloroacetylcarbamoyl derivatives of the general formula (IX) - wherein the meaning of Z is as defined above - are dehydrated to yield the chloroacetylcyano derivatives of the general formula (III). Dehydration is carried out preferably with oxalyl chloride in DMF or with phosphoryl chloride in acetonitrile, at a temperature below 0 °C. ----------



---------- Figure 1. ----------



---------- Figure 2. ----------



---------- Figure 3. ----------

Biological investigations ----------

DPP-IV enzyme inhibitory activities of the compounds with the general formula (I) were determined by the following method: ----------

Applied conditions of the assay: ----------

DPP-IV source: solubilized crude extractum from ---------- CaCo/Tc-7 cells ----------

---------- content: 0.8-1µg/assay ----------

Substrate: H-Gly-Pro-AMC (Bachem) ----------

Reaction: 1 hour preincubation with samples at ---

--------- 37 °C, ----------

--------- 30 min reaction time at 37°C ----------

Stop solution: 1 M Na-acetate buffer (pH = 4.2) --

Reaction mixture: 10 µl of enzyme solution ------- ---------- 10 µl of test compound or assay - ---------- buffer ---------- ---------- 55 µl of assay buffer ---------- ---------- 25 µl of substrate ---------- ---------- 300 µl of stop solution -------- Measurement: spectrofluorometric determination by ---------- Tecan plate reader ---------- ---------- (Ex: 360 nm, Em: 465 nm) ---------- ------- The reaction of the DPP-IV enzyme and the H-Gly-Pro-AMC substrate is recorded by the liberation of AMC (7-amino-4-methyl coumarin) at 37 °C in 100 mM Tris-HCl, pH = 7.5 (assay buffer). Standard curve of AMC is linear up to 31.25 µM concentration, that is why we used the relative fluorescence unit (RFU) of AMC formed. It is detected using 360 nm excitation and 465 emission filters (30 µs integration time, gain 25, No. of flashes 50) by Tecan Spectrofluor Plus plate reader. Under these conditions enzyme reaction is linear for at least 30 min, and the enzyme dependence is linear up to 2.5 µg protein (up to 700 RFU). Using 1-0.8 µg of extracted protein K_m for H-Gly-Pro-AMC is 50 µM. Higher than 500 µM substrate concentration caused fluorescent detection problems (inner fil-

ter effect) that can be solved by dilution of the samples. ----------

------- The assay is designed to detect as efficiently as possible the active inhibitors using a 60 min preincubation time at 37 °C. The assay is conducted by adding 0.8-1 µg of protein extract in 10 µl of enzyme solution (using assay buffer: 100 mM Tris-HCl, pH = 7.5) to the wells containing the test compounds in 10 µl volume and the 55 µl of assay buffer (65 µl of assay buffer in the case of controls). After the preincubation period, the reaction is started by the addition of 25 µl of 1 mM H-Gly-Pro-AMC substrate solution (250 µM final concentration). The final test volume is 100 µl and the test solution contains 1 % DMSO coming from the test compounds solution. Reaction time is 30 min at 37 °C, and the reaction is stopped by adding 300 µl of 1 M Na-acetate buffer, pH = 4.2. The fluorescence (RFU) of AMC formed is detected using 360 nm excitation and 465 emission filters in Tecan spectrofluor Plus plate reader (30 µs integration time, gain 25 No. of flashes 50). ------ Inhibition % are calculated using the RFU of control and RFU of blank. ----------

IC_{50} values characteristic for the enzyme inhibi-

tory effect of the compounds of the general formula (I) according to the invention are lower than 100 nM. The compounds of the general formula (I) and their salts, solvates and isomers can be formulated to orally or parenterally applicable pharmaceutical preparations by known methods, by mixing them with one or more pharmaceutically accepted carriers or auxiliary materials. ----------

The daily dose of the compounds of the general formula (I) depends on several factors, thus on the nature and seriousness of the disease of the patient, on the mode of application and on the compound itself. ----------

Example 1: ----------

3-{[8-(5-Cyanopyridin-2-yl)-8-azabicyclo[3.2.1] --octan-3-yl]-*exo*-amino}acetyl-4-(*R*)- cyanothia- --- zolidine dihydrochloride ----------

------- In the general formula (I) R^1 stands for 5-cyanopyridin-2-yl group, m means 2, Z stands for the group of formula (1). ----------

a.) 3-*exo*-[(*tert*-Butoxycarbonyl)amino]-8-(5-cyano- pyridin-2-yl)-8-azabicyclo[3.2.1]-octane -----

compound of the general formula (V) - wherein m means 2 and Y stands for a $-COOC(CH_3)_3$ group- ------- The solution of 415 mg (3 mmol) of 2-

chloro-5-pyridine, 679 mg (3 mmol) of 3-*exo*-[(*tert*-butoxycarbonyl)amino]-8-azabicyclo[3.2.1]-octane (J.S. Kiely et al. J. Med. Chem. 34, p. 656 (1991)) and 0.46 ml (3.1 mmol) of diazabicyclo[5.4.0]undecene in 25 ml of *n*-pentanol is boiled for 8 hours. The resulting solution is evaporated under vacuum, the residue is dissolved in dichloromethane, washed with water and dried over sodium sulfate. After purification by chromatography (*n*-hexane - ethyl acetate - chloroform 2:1:1) 608 mg (62 %) of title material is obtained. Mp.: 141-143 °C. ^{1}H-NMR (DMSO-d_6): δ 1.38 (s, 9H); 1.44-1.68 (t; 2H); 1.67-2.01 (m, 6H); 3.88 (m, 1H); 4.60 (bs, 2H); 6.61 (d, 1H); 6.80 (d, 1H); 7.81 (dd, 1H); 8.48 (d, 1H). ----------

b.) 3-*exo*-Amino-8-(5-cyanopyridin-2-yl)-8-azabicyclo[3.2.1]octane ----------

compound of the general formula (II) - wherein the meaning of R^1 is the same as given above ----------The solution of 657 mg (2 mmol) of 3-*exo*-[(*tert*-butoxycarbonyl)amino]-8-(5-cyanopyridin-2-yl)-8-azabicyclo[3.2.1]octane in 20 ml of 12 % hydrogen chloride solution in ethanol is stirred at room temperature for 3 hours. To the resulting white suspension 20 ml of water is added to obtain

a solution which is alkalized to pH > 10 with 40 % potassium hydroxide solution and extracted with dichloromethane. The organic layer is dried over sodium sulfate and evaporated. The residue is crystallized from *n*-hexane to obtain 259 mg (57 %) of title compound. Mp.: 123-124 °C. ^{1}H-NMR (DMSO-d_6): δ 1.26 (t, 2H); 1.68-1.93 (m, 6H); 3.12 (m, 1H); 4.57 (b, 2H); 6.78 (d, 1H); 7.79 (dd, 1H); 8.46 (d, 1H). ----------

c.) 3-(*tert*-Butoxycarbonyl)-4-(*R*)-carbamoyl-thiazolidine ----------

compound of the general formula (VII) -

wherein the meaning of Z is as given above; ---

------- 11.1 g (47.6 mmol) of 3-(*tert*-butoxycarbonyl)thiazolidine-4-(*R*)-carboxylic acid is dissolved in 125 ml of dichloromethane and 8 ml (57.5 mmol) of triethylamine is added. To the resulting mixture 5.85 ml (47.6 mmol) of pivaloyl chloride is added dropwise at -15 °C, the mixture is stirred at this temperature for an additional 1 hour, then 12.5 ml of 25 % aqueous ammonia is added and stirring is continued for 1 hour. The reaction mixture is washed consecutively with water, with 1 N NaOH solution and with water, then dried over sodium sulfate. The expected product is

a colourless oil, weighing 5.9 g (88 %). ^{1}H-NMR (DMSO-d_6): δ 1.39 (s, 9H, 3xCH_3); 3.00 and 3.25 (AB q, J = 12.4 Hz, 5-CH_2); 4.32 and 4.57 (AB q, J = 9 Hz, 3-CH_2); 4.3-4.59 (br, 1H, 4-CH); 7.11 and 7.43 (s, 2x1H, NH_2). ----------

d.) Thiazolidine-4-(*R*)-carboxamide hydrochloride - compound of the general formula (VIII) - wherein the meaning of Z is as given above ---------- 9.25 g (39.8 mmol) of 3-(*tert*-butoxycarbonyl)-4-(*R*)-carbamoyl-thiazolidine is dissolved in 45 ml of 25 % hydrogen chloride solution in ethanol and stirred for 5 hours. The resulting white crystals are filtered off, washed with diethyl ether. Yield: 5.42 g (81 %), mp.: 216-217 °C. ^{1}H-NMR (DMSO-d_6): δ 3.04 and 3.46 (q, 2 x 1H, 5-CH_2); 4.28 (q, 2H, 3-CH_2); 4.38 (q, 1H, 4-CH); 7.76 and 8.17 (s, 2x1H, NH_2); 10.09 (broad, 2H, NH_2^+). ----------

e.) 3-Chloroacetyl-4-(*R*)-carbamoyl-thiazolidine -- compound of the general formula (IX) - wherein the meaning of Z is as given above ---------- To the suspension of 8.83 g (52.3 mmol) of thiazolidine-4-(*R*)-carboxamide hydrochloride in 180 ml of dichloromethane 14.7 ml (105 mmol) of triethylamine, then a solution of 4.46 ml (56

mmol) of chloroacetyl chloride in 20 ml of dichloromethane is added dropwise at 0 °C. The mixture is stirred for 30 minutes, allowed to warm to room temperature, then stirred for additional 2 hours. The resulting mixture is extracted with 3 × 200 ml of water, the united aqueous layers are concentrated under vacuum to ~ 1/3 of its volume and made alkaline with 20 % NaOH solution. The expected product precipitates in the form of white crystals. Yield: 8.12 g (75 %), mp.: 119-121 °C. ^{1}H-NMR (DMSO-d_6): δ 3.05 and 3.23 (q, 2 x 1H, 5-CH_2); 4.39-4.54 (m, 3H, 3-CH_2 +4-CH); 4.71 (d, 2H, CH_2Cl); 7.20 and 7.43 (s, 2x1H, NH_2). ----------

f.) 3-Chloroacetyl-4-(*R*)-cyanothiazolidine -------

compound of the general formula (III) -

wherein the meaning of Z is as given above ---

------- 7.78 g (37.3 mmol) of 3-chloroacetyl-4-(R)-carbamoyl-thiazolidine is suspended in 65 ml of dry acetonitrile, to the suspension 3.7 ml of dry dimethylformamide, then at -10 °C, the solution of 3.51 ml (40.6 mmol) of oxalyl chloride in 8 ml acetonitrile is added dropwise. The mixture is stirred for 1 hour and 6.6 ml of dry pyridine is dropped to it. After 1 hour of stirring the mixture is evaporated to dryness, the residue is

mixed with water and extracted with dichloromethane. The united organic layers are washed with 1:1 aqueous hydrochloric acid, then with water. After drying and evaporation the expected product crystallizes from ethanol: 3.09 g (43 %). Mp: 106-108 °C. ^{1}H-NMR ($CDCl_3$): δ 3.33 (d, 2H, 5-CH_2); 4.14 (s, 2H, 3-CH_2); 4.69 (q, 2H, $ClCH_2$); 5.27 (s, 1H, 4-CH). ----------

g.) 3-{[8-(5-Cyanopyridin-2-yl)-8-azabicyclo [3.2.1]octan-3-yl]-*exo*-amino}acetyl-4-(*R*)-cyanothiazolidine dihydrochloride ----------

------- 114 mg (0.6 mmol) of 3-*exo*-amino-8-(5-cyanopyridin-2-yl)-8-azabicyclo[3.2.1]octane and 114 mg (0.815 mmol) of 3-chloroacetyl-4-(*R*)-cyanothiazolidine are dissolved in 20 ml of acetonitrile and to the solution 460 mg (1.125 mmol) of PBEMP is added. The mixture is stirred at 55 °C for 16 hours, the scavenger resin is filtered off and the filtrate is evaporated. The residue is purified by chromatography using $CHCl_3$-MeOH 9:1 mixture eluent. After acidification with hydrogen chloride solution in ethanol and precipitation with diethyl ether the title compound is obtained in the form of white crystals: 75 mg (32 %), mp: 204-206 °C. ^{1}H-NMR (DMSO-d_6): δ 1.70-1.78 (m, 4H);

2.01 (m, 4H); 3.37 (m, 2H); 3.67 (m, 1H); 4.07 (m, 1H); 4.21 (m, 1H); 4.56 (d, 1H); 4.76-4.79 (m, 3H); 5.33 (m,1H); 6.89 (d, 1H); 7.91 (dd, 1H); 8.53 (d, 1H); 9.01 (bs, 2H). ----------

Example 2: ----------

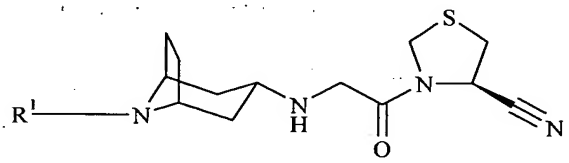
3-{[8-(Pyrazin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl]-*exo*-amino}acetyl-4-(*R*)-cyanothiazolidine dihydrochloride ----------

------- 107 mg (0.52 mmol) of 3-*exo*-amino-8-(pyrazin-2-yl)-8-azabicyclo[3.2.1]octane and 86 mg (0.45 mmol) of 3-chloroacetyl-4-(*R*)-cyanothiazolidine are dissolved in 15 ml of acetonitrile and to the solution 0.21 ml (1.5 mmol) of triethylamine is added. The mixture is stirred for 4 hours at 75 °C then evaporated under vacuum. The residue is purified by chromatography using $CHCl_3$-MeOH 6:1 mixture eluent. After acidification with hydrogen chloride solution in ethanol and precipitation with diethyl ether, the title compound is obtained in the form of white crystals: 37 mg (19 %), mp: 165-170 °C. ^{1}H-NMR (DMSO-d_6): δ 1.76-1.80 (m, 4H); 1.95-2.01 (m, 4H); 3.35 (m, 2H); 3.63 (m, 1H); 4.05 (m, 1H); 4.18 (m, 1H); 4.57 (d, 1H); 4.67 (s, 2H); 4.78 (d, 1H); 5.32 (dd, 1H); 7.87 (d, 1H); 8.15 (dd, 1H); 8.28 (d, 1H); 8.99 (bs,

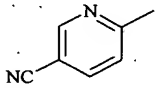
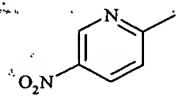
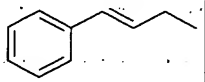
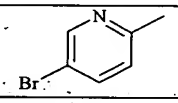
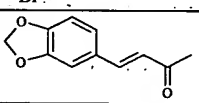
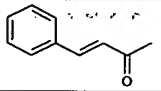
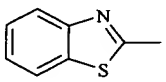
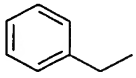
2H). ----------

Example 3: ----------

In a similar manner as described in Examples 1 and 2 the following compounds of the general formula (I) have been prepared: ----------



---------- Table 1 ----------

R^1	M.p. or ^{1}H-NMR (DMSO-d_6, aromatic protons)	IC_{50} (nM)
	(from the *endo*-amine); 163-166 °C	6
	2HCl; 190-191 °C	8
	130-134 °C	12
	156-158 °C	15
	87-90 °C	18
	85-88 °C	22
	2HCl; 262-265 °C	
	7.27-7.42 (m, 5H);	

Example 4: ----------

1-{[8-(5-Nitropyridin-2-yl)-8-azabicyclo[3.2.1] -- octan-3-yl]-*exo*-amino}acetyl-2-(*S*)-cyanopyr- ----- rolidine ----------

------- 297 mg (1.2 mmol) of 3-*exo*-amino-8-(5-nitropyridin-2-yl)-8-azabicyco[3.2.1]octane is reacted with 172 mg (1 mmol) of 1-chloroacetyl-2-(*S*)-cyanopyrrolidine, in 20 ml of acetonitrile in the presence of 0.41 ml (3 mmol) of triethylamine, as described in Example 2. After processing and chromatographic purification the product is crystallized from ethyl acetate: 116 mg (30 %). Mp.: 151-163 °C. ^{1}H-NMR (DMSO-d_6): δ 1.34 (t, 2H); 1.88 (m, 3H); 1.93-2.01 (m, 6H); 2.11 (m, 2H); 3.07 (m, 1H); 3.32 (m, 1H); 3.38 (m, 1H); 3.55 (m, 1H); 4.50 (b, 1H); 4.71 (m, 1H); 4.92 (b, 1H); 6.81 (d, 1H); 8.20 (dd, 1H); 8.97 (d, 1H). ----------

Example 5: ----------

------- In a similar manner as described in Example 4 the following compounds of the general formula (I) have been prepared: ----------

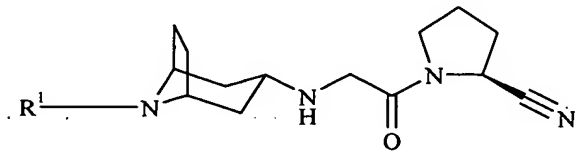
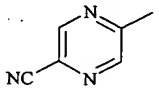
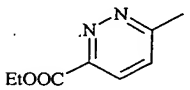
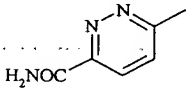
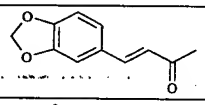
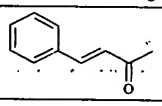
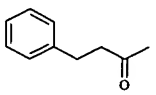
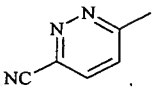
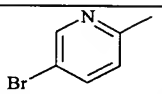
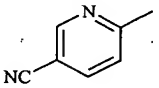
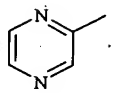
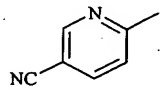
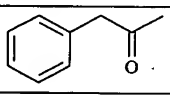
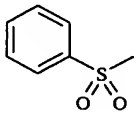
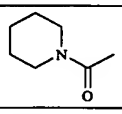
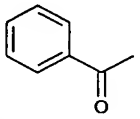
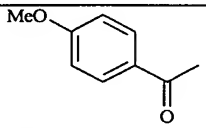
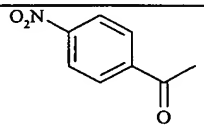
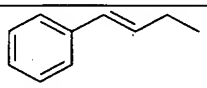
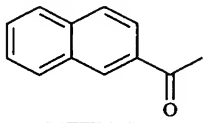
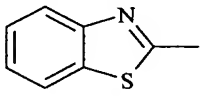


Table 2

R^1	M.p. or ^{1}H-NMR (DMSO-d_6, aromatic protons)
	96-97 °C
	190-191 °C
	HCl; amorphous solid;
	83-86 °C
	60-63 °C
	HCl: 77-80 °C
	HCl; 105-107 °C
	65-66 °C
	2HCl 220-223 °C
	2HCl; 172-174 °C
	(from the *endo*-amine); 141-143 °C
	151-153 °C

	46-49 °C
	102-104 °C
	65-67 °C
	52-55 °C
	86-89 °C
	88-90 °C
	70-75 °C
	2HCl; 266-269 °C

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---------- **Claims** ----------

1. Compounds of the general formula (I) - wherein

R^1 stands for ----------

- a nitrogen-containing one- or two-membered aromatic rings, preferably a pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, imidazolyl, pirazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, quinolinyl, isoquinolinyl, cinno-

linyl, phthalazinyl, quinazolinyl, quinoxalinyl, benzimidazolyl, indazolyl, benzothiazolyl, benzisothiazolyl, benzoxazolyl or benzisoxazolyl group; optionally mono- or disubstituted independently by one or two of the following groups: C1-4 alkyl group, C1-4 alkoxy group, a halogen atom, a trihalogenomethyl group, methylthio group, nitro group, cyano group, or; ----------

- an R_{1a}-CH_2-group, where the meaning of R_{1a} is a hydrogen, a C1-4 alkyl group or phenyl, benzyl, phenylethyl, phenylethenyl, naphthyl, pyridyl, quinolyl, isoquinolyl, cinnolinyil, phthalazinyl, quinazolinyl, quinoxalinyl, thienyl, furyl or *p*-tolylsulfonyl groups substituted independently by one or more C1-4 alkyl, C1-4 alkoxy, alkylenedioxy, halogen, trihalogenomethyl, nitro or cyano group, or ----------

- an R_{1b}-CO-group, where the meaning of R_{1b} is C1-4 alkyl group, phenyl, benzyl, phenylethyl, phenylethenyl, naphthyl, pyridyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl or quinoxalinyl groups substituted independently by one or more C1-4 alkyl, C1-4 alkoxy, alkylenedioxy, halogen, trihalogenomethyl, nitro or cyano group; mono- or disubstituted amino group,

saturated *N*-containing heterocyclic ring, preferably a group containing pyrrolidine, piperidine, piperazine or morpholine ring, ----------

- m means 2 or 3, ----------

- Z stands for a groups of formula (1), (2), (3), (4), (5), (6), (7) or (8), - and the salts, isomers or solvates thereof. ----------

2. Compounds of the general formula (I) as defined in claim 1 - wherein R^1 means a pyridyl or pyrazinyl group substituted with a nitro or cyano group, n means 2 and Z means a group of formula (1) or (2) - as well as their salts isomers and solvates. ----------

3. 3-{[8-(5-Cyanopyridin-2-yl)-8-azabicyclo [3.2.1]octan-3-yl]-*exo*-amino}acetyl-4-(*R*)-cyanothiazolidine; ----------

4. 3-{[8-(Pyrazin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl]-*exo*-amino}acetyl-4-(*R*)-cyanothiazolidine; ----------

5. 1-{[8-(5-Nitropyridin-2-yl)-8-azabicyclo [3.2.1]octan-3-yl]-*exo*-amino}acetyl-2-(*S*)-cyanopyrrolidine; ----------

6. Pharmaceutical preparation characterized by containing a compound of the general formula (I) - wherein the meanings of R^1,

m and Z are the same as defined in Claim 1 - or isomers or solvates thereof, in the form of the free compound or of a salt, and at least one pharmaceutically accepted carrier material or diluent. ----------

7. A process for the preparation of the compounds of the general formula (I) - wherein the meanings of R^1, m and Z are the same as defined in Claim 1 - characterized by reacting a compound of the general formula (II) - wherein the meaning of R^1 is as defined above - with a compound of the general formula (III) - wherein the meaning Z is as defined above - and separating the resulting compound of the general formula (I) or its salt from the reaction mixture. ----------

8. Application of a compound of the general formula (I) - wherein the meanings of R^1, m and Z are as defined in Claim 1 - for the production of pharmaceutical preparations suitable to inhibit the DPP-IV enzyme activity, thus suitable to treat diseases related with DPP-IV enzyme concentration. ----------

9. A process for the inhibition of the DPP-IV enzyme and for treatment of diseases related

with the DPP-IV enzyme concentration, characterized by applying a compound of the general formula (I) as defined in Claim 1 in therapeutically effective quantity, in the form of the free compound, or of its salt. ---

10. Compounds of the general formula (II) - wherein the meanings of R^1 and m are as defined in Claim 1 - and their salts. ----------

11. Compounds of the general formula (V) - wherein the meaning of R^1 is as defined in Claim 1 and Y means a *tert*-butoxycarbonyl group. ---------

12. Compounds of the general formula (VII) - wherein the meaning of Z is as defined in Claim 1. ----------

13. Compounds of the general formula (VIII) - wherein the meaning of Z is as defined in Claim 1 - and their salts. ----------

14. Compounds of the general formula (IX) - wherein the meaning of Z is as defined in Claim 1. ----------

15. Compounds of the general formula (III) - wherein the meaning of Z is as defined in claim 1. ----------

The Representative in the name of the Applicant: --

L.S.: sanofi-synthelabo ----------

L.S.: CHINOIN Rt. ----------

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New Compounds ----------

---------- 4/1

Applicant: Sanofi-Synthelabo, Paris, France ------

L.S.: sanofi-synthelabo ----------

L.S.: CHINOIN Rt. ----------

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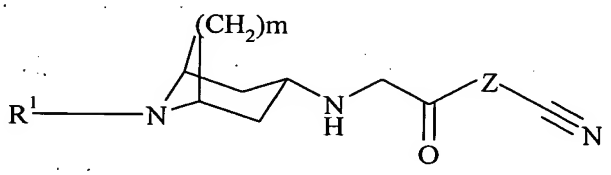

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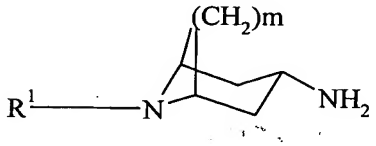

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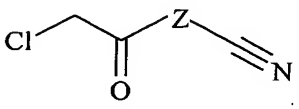

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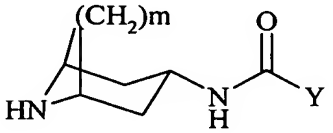

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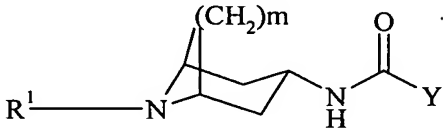

(V)

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New Compounds ----------

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Applicant: Sanofi-Synthelabo, Paris, France ------

L.S.: sanofi-synthelabo ----------

L.S.: CHINOIN Rt. ----------

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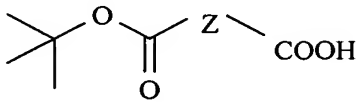

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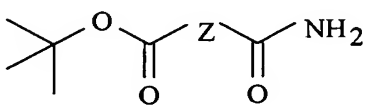

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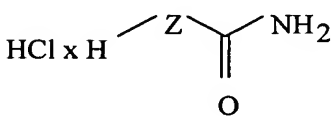

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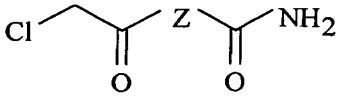

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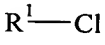

(X)

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New Compounds ----------

---------- 4/3

Applicant: Sanofi-Synthelabo, Paris, France ------

L.S.: sanofi-synthelabo ----------

L.S.: CHINOIN Rt. ----------

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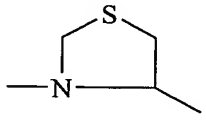

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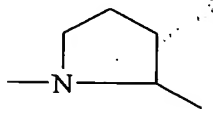

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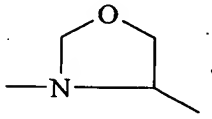

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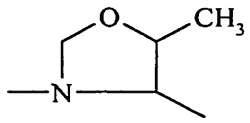

(4)

(5)

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New Compounds ----------

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Applicant: Sanofi-Synthelabo, Paris, France ------

L.S.: sanofi-synthelabo ----------

L.S.: CHINOIN Rt. ----------

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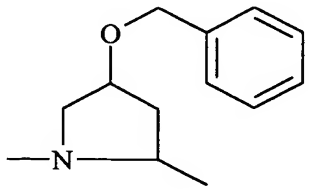

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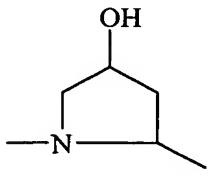

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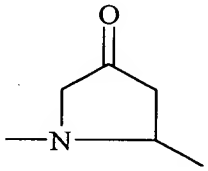

(8)

04/KO-75178 OFFI - Hitelesen bizonyítom, hogy ez a fordítás az eredeti anyaggal mindenben megegyezik.
Budapest, 2004. november 18. ----------
Az Országos Fordító és Fordításhitelesítő Iroda igazgatója helyett ----------

No. 04/KO-75178 ----------
The Hungarian National Office for Translations and Attestations hereby officially certifies that the above translation is in full conformity with the original. ----------
Budapest, 18th November, 2004 ----------
for the Director ----------